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COX-2 Inhibition, *H. pylori* Infection and the Risk of Gastrointestinal Complications

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Abstract: Current data on the gastric safety of cyclooxygenase-2 (COX-2) inhibitors in the presence of *H. pylori* infection are largely derived from animal experiments and indirect clinical evidence. In animal models of *H. pylori* gastritis, COX-2 inhibitors suppressed prostaglandin synthesis and aggravated mucosal damage. In the human stomach, COX-1 appears to be the predominant source of prostaglandins despite the fact that COX-2 is upregulated in *H. pylori* gastritis. There are conflicting data on whether *H. pylori* alters the risk of ulcer in patients receiving COX-2 inhibitors. Among patients with *H. pylori* infection, rofecoxib reduced the risk of complicated gastric but not duodenal ulcers as compared to naproxen. The advantage of rofecoxib over naproxen also disappeared in patients with *H. pylori* infection and prior upper gastrointestinal events. In contrast, pooled data suggested that *H. pylori* increases the risk of ulcer in patients receiving nonselective nonsteroidal anti-inflammatory drugs but not in patients receiving celecoxib. In rodent gastric ulcers, COX-2 was upregulated in the granulation tissue and ulcer margin. Inhibition of COX-2 delayed healing of experimental gastric ulcer. Limited data showed that COX-2 expression was also increased in human gastric ulcer regardless of the *H. pylori* status. The functional significance of COX-2 in human gastric ulcer is unknown.

Key Words: *H. pylori*, cyclooxygenase-2, COX-2 inhibitors, prostaglandins, ulcer.

INTRODUCTION

Helicobacter pylori and nonsteroidal anti-inflammatory drugs (NSAIDs) are the two most important causes of gastroduodenal ulcer disease worldwide. Since many NSAID users are infected with *H. pylori*, it is important to determine whether *H. pylori* would influence the risk of developing ulcers in these patients. It is generally thought that *H. pylori* and NSAIDs are independent risk factors for ulcer disease because they damage the gastric mucosa via different mechanisms. *H. pylori* induces proinflammatory cytokines, leading to mucosal inflammation and epithelial injury. In contrast, NSAIDs damage the gastric mucosa by inhibiting gastric prostaglandin synthesis. However, this view may be simplistic because *H. pylori* and NSAIDs share certain pathways in the pathogenesis of mucosal injury [1, 2]. The controversy about the role of *H. pylori* in NSAID-associated gastroduodenal damage hinges on whether the effects of *H. pylori* and NSAIDs on gastric mucosal damage is synergistic, additive, or antagonistic, and whether there is sufficient clinical evidence to draw any conclusion. Current data suggest that *H. pylori* infection probably has a diverse effect on the gastric mucosa in different subgroups of NSAID users, which partly accounts for the conflicting results on the interaction between *H. pylori* and NSAIDs in mucosal damage [1, 2].

Development of NSAIDs that selectively inhibit cyclooxygenase-2 (COX-2) offers the prospect of relieving pain and inflammation without inflicting gastric injury. In healthy volunteers, selective inhibition of COX-2 does not suppress gastric prostaglandins [3]. There is good clinical evidence that COX-2 specific inhibitors cause fewer clinical upper gastrointestinal events compared with nonselective NSAIDs [4, 5]. However, the gastrointestinal safety of COX-2 specific inhibitors in the presence of mucosal inflammation remains unclear. COX-2 is induced in gastrointestinal inflammatory conditions, such as inflammatory bowel disease and *H. pylori* gastritis. Inhibition of COX-2 has been shown to suppress colonic prostaglandin synthesis in ulcerative colitis and Crohn's disease [6, 7]. In the rat colitis model, COX-2 specific inhibitor exacerbates colonic inflammation [8]. In the stomach, *H. pylori* induces mucosal inflammation and has been shown to upregulate the expression of COX-2 [1, 6, 7, 9, 10]. This raises the possibility that COX-2 may be the predominant source of prostaglandins in *H. pylori* gastritis, leading to an increased susceptibility to mucosal injury by COX-2 specific inhibitors. To date there are conflicting data showing that COX-2 specific inhibitors increase or have no effect on the risk of mucosal injury in the presence of *H. pylori* gastritis. How COX-2 specific inhibitors differ from nonselective NSAIDs in terms of their effects on *H. pylori*-infected gastric mucosa will be an interesting area of research.

Expression and Cellular Localization of COX-2 in *H. pylori* Infection

Many studies have reported an increased expression of COX-2 in the presence of *H. pylori* infection. *H. pylori* has been shown to upregulate the expression of COX-2 messenger RNA (mRNA) and stimulates prostaglandin synthesis in gastric cancer cell lines [11]. However, there are conflicting data on the cellular localization of COX-2 expression in *H. pylori* gastritis. Fu *et al.* reported that *H. pylori* induces COX-2 expression in the mononuclear

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inflammatory cells and myofibroblasts in the lamina propria [10]. However, other studies found that COX-2 was expressed mainly in the gastric epithelium [1, 6, 7]. Sawaoka *et al.* reported that COX-2 was expressed both in the gastric epithelium and subepithelial inflammatory cells in *H. pylori* gastritis [9]. These inconsistent immunohistochemical findings probably are related to different laboratory conditions and cross-reactivity of COX-2 antibodies with other mucosal antigens. Using in situ hybridization, it has been shown that *H. pylori* up-regulates the expression of COX-2 mRNA mainly in the gastric epithelial cells [1].

Role of COX-1 and COX-2 in *H. pylori*-Induced Prostaglandin Synthesis

In the normal human stomach, COX-2 is absent or minimally expressed whereas COX-1 is the source of prostaglandins that maintains the integrity of the mucosal barrier. This notion is consistent with the observation that in the absence of *H. pylori* infection, inhibition of COX-2 did not suppress gastric prostaglandin synthesis and inflicted minimal mucosal injury [3]. However, in cultured human gastric fibroblasts [12, 13], *H. pylori* induced the expression of COX-2 mRNA and increased prostaglandin synthesis. Indomethacin and a COX-2 inhibitor (NS-398) suppressed *H. pylori*-induced prostaglandin synthesis to the same extent. These findings suggested that COX-2 may substantially contribute to prostaglandin synthesis in *H. pylori* gastritis, and that selective inhibition of COX-2 may lose its gastric sparing effect in the presence of *H. pylori* infection.

However, there were conflicting data on the relative contributions of COX-1 and COX-2 in prostaglandin synthesis associated with *H. pylori* gastritis. Jackson *et al.* [14] reported that COX-1 and COX-2 were constitutively expressed in parietal cells of uninfected human stomach. Immunostaining for both COX-1 and COX-2 was increased in *H. pylori* gastritis. Interestingly, the increased *ex vivo* prostaglandin synthesis was significantly suppressed by a COX-1 inhibitor rather than a COX-2 inhibitor. Scheiman *et al.* studied the effect of rofecoxib on gastric prostaglandin synthesis in subjects with or without *H. pylori* infection [15]. Twenty *H. pylori*-infected and 6 uninfected healthy volunteers were treated with rofecoxib for 2 weeks. Although prostaglandin levels were increased in *H. pylori* gastritis, rofecoxib did not suppress prostaglandin synthesis in infected subjects. These results suggested that despite an upregulation of COX-2, *H. pylori* gastritis, COX-1 remains the predominant source of prostaglandins.

EFFECTS OF NSAIDS AND COX-2 SPECIFIC INHIBITORS ON *H. pylori*-INFECTED GASTRIC MUCOSA

Gastric prostaglandins play a crucial role in mucosal defense by regulating mucosal blood flow, mucus and bicarbonate secretion, epithelial proliferation, epithelial restitution, and mucosal immunocyte function [16]. The fact that *H. pylori* infection stimulates gastric prostaglandin production has led to the speculation that *H. pylori* may alleviate mucosal injury induced by NSAIDs. However, administration of NSAIDs to *H. pylori*-infected subjects has been shown to profoundly suppress prostaglandin production to levels that were similar to those of uninfected subjects [17, 18]. These findings indicate that the modest increase in prostaglandin levels induced by *H. pylori* is unlikely to have any important protective effect against NSAID injury. It has been postulated that the mucosal toxicity of *H. pylori*, which is largely mediated by inflammatory cytokines including interleukin (IL)-1, IL-6, IL-8 and tumor necrosis factor, is counterbalanced by protective responses, such as increased release of mucosal prostaglandins and hepatocyte growth factor [12]. Factors disturbing this balance may enhance the gastric damaging effects of NSAIDs and mucosal toxicity of *H. pylori* [12]. To date there are only a few experimental and human studies investigating the effects of selective COX-2 inhibition on *H. pylori*-infected gastric mucosa.

Animal Studies (Table 1)

Several studies have investigated the effect of nonselective NSAIDs and a COX-2 specific inhibitor on *H. pylori* gastritis using the Mongolian gerbil model [13, 19, 20]. In one study [13], COX-1 was detected in both normal and *H. pylori*-infected mucosa whereas COX-2 was expressed only in the infected mucosa. *H. pylori* infection increased prostaglandin synthesis. Indomethacin markedly inhibited prostaglandin synthesis in both normal and infected mucosa. NS-398 also suppressed prostaglandin synthesis in infected mucosa but did not have any effect on uninfected mucosa. Hemorrhagic erosions and neutrophil infiltration were found in *H. pylori* gastritis. These mucosal lesions were aggravated by indomethacin and NS-398. Both drugs potentiated the release of neutrophil chemokine and interferon-γ induced by *H. pylori*. In another study [19], indomethacin and NS-398 significantly suppressed gastric prostaglandin synthesis and there was a non-significant trend toward less severe suppression with NS-398 in *H. pylori*-infected gerbils. Indomethacin and NS-398 caused similar degree of gastric mucosal damage in infected animals despite

Table 1. Effects of NSAIDs and COX-2 Inhibitor on Animal Models of *H. pylori* Gastritis

Animal model	COX-1 & -2 expression	Baseline PGE2	PGE2 after NSAIDs	PGE2 after COX-2 inhibitor
Mongolian Gerbil [13]	COX-2 upregulated	Increased	Suppressed	Moderately suppressed*
Mongolian Gerbil [19]	---	Increased	Suppressed	Moderately suppressed†
Mouse [21]	COX-1 & -2 upregulated	Non-significant increase	Suppressed	Non-significant decrease

*Mucosal damage was aggravated by both NSAIDs and NS-398 in *H. pylori*-infected mucosa.
†NSAIDs and NS-398 induced similar degree of mucosal damage in *H. pylori*-infected animals.

different degrees of prostaglandin suppression. In contrast, there was an inverse relationship between gastric prostaglandin level and mucosal damage in uninfected animals. These findings suggested that while COX-2 specific inhibitors caused minimal injury to uninfected gastric mucosa, these drugs did not reduce mucosal damage in *H. pylori* gastritis.

Unlike the previous two studies, Kim *et al.* [21] found that both COX-1 and COX-2 were upregulated in mouse stomachs infected with *H. pylori*. *H. pylori* infection increased apoptotic index, cell proliferation index, neutrophil activity and the degree of chronic inflammation. There was a non-significant increase in gastric prostaglandin levels. All these changes were reversed after the administration of indomethacin whereas NS-398 did not induce a significant reduction. The result suggested that both COX-1 and COX-2 are induced by *H. pylori* infection. Induction of COX-1 also contributes to the increase in prostaglandin synthesis, mucosal cell turnover and inflammatory activity in *H. pylori* gastritis.

Recently, Futagami *et al.* [20] investigated how inhibition of COX-2 would influence the severity of NSAID-induced gastric damage in *H. pylori*-infected Mongolian gerbils. *H. pylori* infection induced COX-2 expression. Prolonged treatment with indomethacin caused more severe gastric damage in *H. pylori*-infected animals than in uninfected animals. Interestingly, pretreatment with NS-398 aggravated the mucosal damage induced by short-term treatment with indomethacin in the presence of *H. pylori*. The authors postulated that induction of COX-2 by *H. pylori* might protect the gastric mucosa against NSAID injury. Disturbance of this equilibrium state by inhibiting COX-2 may enhance the gastric toxicity of NSAIDs in *H. pylori*-infected animals (Fig. **1**).

Human Studies (Table 2)

Current evidence on the gastric safety of COX-2 inhibitors in *H. pylori*-infected patients is mostly derived from *post hoc* analysis. Whether *H. pylori* infection increases the risk of ulcer disease in patients receiving COX-2 specific inhibitors has generated conflicting results in the literature.

The influence of *H. pylori* infection on the risk of gastroduodenal ulceration was first reported in a subgroup analysis of a double-blind, 12-week endoscopic study of celecoxib versus naproxen [22]. Among patients who received celecoxib, the incidence of ulcer was 12.9% in patients with *H. pylori* infection compared with 2.9% in uninfected patients (P=0.023). Other risk factors included concurrent use of low-dose aspirin (P=0.001) and a history of ulcer (P=0.010). In contrast, *H. pylori* did not influence the risk of ulcer among patients who received naproxen. However, the same group of investigators reported contradictory results in a pooled analysis of four double-blind 12-week endoscopic studies of celecoxib that collectively enrolled 4000 arthritis patients [23]. Among patients who used nonselective NSAIDs, the incidence of ulcer was 28.4% in patients with *H. pylori* infection compared with 20% in uninfected patients (odds ratio 1.6 [1.1, 2.3]). Among patients who used celecoxib, the incidence of ulcer was 8.0% in patients with *H. pylori* infection compared with 5.1% in uninfected patients (odds ratio 1.6 [0.9, 2.8]). These results suggested that *H. pylori* is a risk factor for gastroduodenal ulceration in patients taking nonselective NSAIDs but not celecoxib.

In a multivariate analysis of risk factors for upper gastrointestinal clinical events [24] based on the data collected in the Vioxx Gastrointestinal Outcomes Research Study [5], major risk factors for the development of upper gastrointestinal clinical events included old age (≥75) and prior complicated or uncomplicated gastrointestinal events. Patients with prior gastrointestinal events who received naproxen had a high rate of clinical events regardless of *H. pylori* status. Although *H. pylori* was not considered as a risk factor in this multivariate analysis, two interesting findings were reported. First, patients in the rofecoxib group had

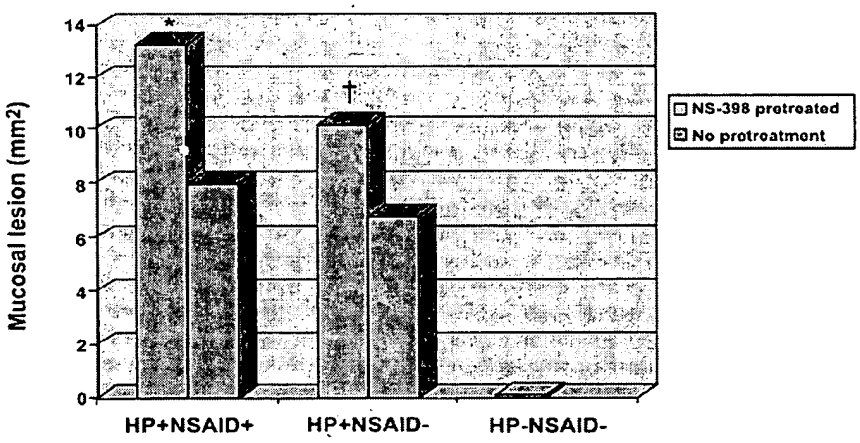

Fig. (1). Effects of Indomethacin on gastric damage in *H. pylori*-infected Mongolian gerbils with or without pretreatment with NS-398. HP and NSAID denote *H. pylori* and indomethacin, respectively. *P<0.05 versus HP+NSAID+ group without pretreatment with NS-398. †P<0.05 versus HP+NSAID- group without pretreatment with NS-398. Data derived from [20].

Table 2. Clinical Effects of *H. pylori* Infection on Gastroduodenal Damage of COX-2 Specific Inhibitors

Design	Number of patients	Outcomes			
Subgroup analysis of a 12-week RCT of celecoxib 400 mg versus naproxen 1 g [22]	536	Endoscopic ulcer:			
			Celecoxib	Naproxen	
		HP positive	12.9%*	29%	
		HP negative	2.9% (P=0.023)*	30%	
Pooled analysis of four 12-week RCTs of celecoxib 100-800 mg versus nonselective NSAIDs [23]	4000	Endoscopic ulcer (non-aspirin users):			
			Celecoxib	Nonselective NSAIDs	
		HP positive	8.0%	28.4%	
		HP negative	5.1%	20.0%	
		OR	1.6 (0.9 - 2.8)	1.6 (1.1 – 2.3)*	
Multivariate analysis of a RCT of rofecoxib 50 mg versus naproxen 1 g [24]	8076	Clinical upper GI events (per 100 patient-years):			
			Rofecoxib	Naproxen	
		Prior event, HP positive	12.18	14.00	RR 0.89 (0.38-2.07)†
		Prior event, HP negative	3.35	17.14	RR 0.20 (0.07-0.61)
		Complicated DU (per 100 patient-years):			
			Rofecoxib	*Naproxen*	
		HP positive	1.85	1.54	RR 1.20 (0.64-2.24)‡
		HP negative	0.34	1.41	RR 0.24 (0.09-0.64)

**H. pylori* was a risk factor in patients taking nonselective NSAIDs but not in patients taking celecoxib

†The upper GI sparing effect of rofecoxib was offset by the presence of *H. pylori* infection in patients with prior upper GI events.

‡The superiority of rofecoxib over naproxen in reducing the risk of complicated duodenal ulcers disappeared in the presence of *H. pylori* infection.

fewer gastric ulcers than patients in the naproxen group regardless of the *H. pylori* status. In contrast, rofecoxib did not reduce the risk of duodenal ulcers compared with naproxen among patients found positive for *H. pylori.* Second, among those with prior gastrointestinal events, the rate of events in the rofecoxib group was 3.5-fold higher in *H. pylori*-positive patients than in *H. pylori*-negative patients. The results suggested that the upper GI sparing effect of rofecoxib was the offset by the presence of *H. pylori* infection in patients with prior upper GI events, and the superiority of rofecoxib over naproxen in reducing the risk of complicated duodenal ulcers disappeared in the presence of *H. pylori* infection.

EFFECTS OF *H. pylori* ON ULCER HEALING ASSOCIATED WITH NSAIDS AND COX-2 SPECIFIC INHIBITORS

Whether *H. pylori* infection affects ulcer healing in patients receiving nonselective NSAIDs has yielded conflicting data. In the rat model, one study found that *H. pylori* attenuated the delay in ulcer healing induced by aspirin. This observation was attributed to suppression of acid secretion and stimulation of prostaglandin production by *H. pylori* [25]. However, there are conflicting findings about the effects of *H. pylori* on aspirin-induced gastric injury. The same group of investigators showed that *H. pylori* induced persistent mucosal bleeding in the rat stomach by impairing gastric adaptation to aspirin [18]. Eradication of *H. pylori* restores gastric adaptation to resist aspirin-induced injury. Hawkey *et al.* studied the effect of *H. pylori* eradication on gastroduodenal damage in chronic NSAID users with dyspepsia or ulcer [26]. In a subgroup of 41 patients with gastric ulcers, they found that eradication of *H. pylori* delayed ulcer healing (ulcer healing at 8 weeks: 72% in the eradicated group compared with 100% in the control group). In another randomized trial of *H. pylori*-positive patients with NSAID-associated ulcer bleeding, 195 patients (112 gastric ulcers and 83 duodenal ulcers) were randomly assigned to receive omeprazole or omeprazole plus eradication therapy for ulcer healing. Eradication of *H. pylori* did not have any significant adverse effect on the healing of gastric (*H. pylori*-positive versus *H. pylori*-eradicated: 94% versus 88%; p=0.29) or duodenal (*H. pylori*-positive versus *H. pylori*-eradicated: 100% versus 98%; p=1.0) ulcers [27] (Fig. 2). To date there is no definite evidence to show that eradication of *H. pylori* has any clinically important adverse effect on healing of NSAID-associated ulcers.

On the other hand, there are data suggesting that among patients receiving NSAIDs, gastric ulcers heal faster with *H. pylori* infection by acid suppression [28, 29]. *H. pylori* infection has been shown to augment the acid-suppressing effect of omeprazole [30, 31]. In a pooled analysis of three randomized trials of omeprazole for the prevention of mucosal injury in NSAID users [28], *H. pylori* appeared to enhance gastric ulcer healing by acid suppression but retard

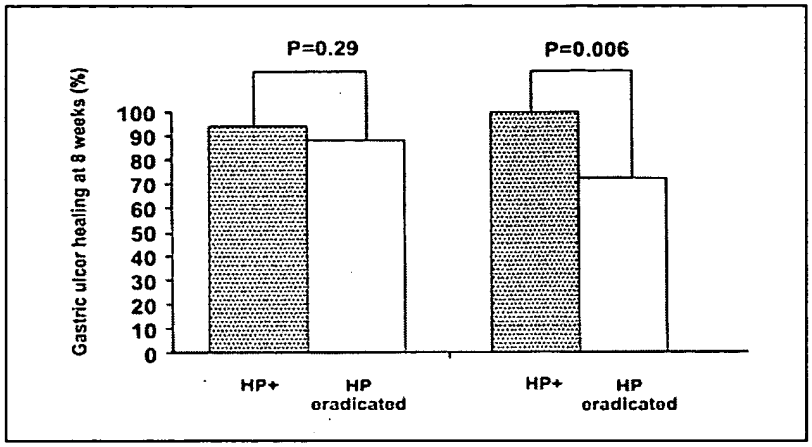

Fig. (2). Effects of *H. pylori* eradication on healing of gastric ulcers in patients receiving nonselective NSAIDs.

healing by misoprostol. However, the difference only reached statistical significance in patients receiving ranitidine (84% vs 51% at eight weeks) but not in patients receiving omeprazole. In another pooled analysis of two randomized trials of lansoprazole versus ranitidine in preventing NSAID-induced mucosal injury [29], gastric ulcer healing rates were significantly faster in *H. pylori*-positive patients than in uninfected patients though the difference was of doubtful clinical relevance (70% vs 61% at 8 weeks; $P < 0.05$).

Although COX-2 specific inhibitors inflict minimal gastric injury to the normal stomach, there is evidence from animal experiments that COX-2 may play a physiological role in restoring mucosal integrity. In the rat stomach, COX-2 was upregulated in acetic acid-induced gastric ulcers [32, 33]. COX-2 activity was detected in endothelial cells, macrophages and fibroblasts at the ulcer base [32, 33]. Selective inhibition of COX-2 has been shown to retard gastric ulcer healing [33-36]. Administration of NS-398 significantly retarded healing of acetic acid-induced ulcers in rats and thermal-cauterized ulcers in mice [33-35]. One study showed that inhibition of COX-2-derived prostaglandins in ulcerated mucosa delayed ulcer healing [33]. Other investigators found that angiogenesis and maturation of granulation tissue in gastric ulcer was impaired by inhibition of COX-2 [36]. Jones *et al.* [37] demonstrated that both nonselective NSAIDs and COX-2 inhibitors acted on endothelial cells to inhibit angiogenesis. In contrast, COX-1 was absent [36] or not induced in ulcerated mucosa [33, 34].

Unlike rodent ulcers, To *et al.* [38] found that both COX-1 and COX-2 were upregulated in human gastric ulcers. At the ulcer margin, increased COX-1 expression was detected in lamina propria cells whereas COX-2 was strongly expressed in the hyperplastic foveolar epithelium. At the ulcer base, COX-1 and COX-2 were strongly expressed in myofibroblasts, macrophages and endothelial cells in the granulation tissue. The findings were similar between *H. pylori* ulcers or NSAIDs ulcers. This raises the possibility that both isoforms of COX may contribute to ulcer healing in the human stomach regardless of the *H. pylori* status. However, other investigators found that although intense COX-2 immunoreactivity was detected in human gastric ulcers, there was no significant change in COX-1 expression in ulcerated mucosa [14, 39]. To date there is no clinical data as to whether COX-2 inhibitors would retard gastric ulcer healing.

CONCLUSION

Current data on the interaction between *H. pylori* infection and selective COX-2 inhibition with respect to gastric damage are mostly derived from animal experiments or indirect clinical evidence based on *post hoc* analysis. Several interesting findings deserve further studying. In animal models of *H. pylori* gastritis, COX-2 inhibitors suppressed prostaglandin synthesis and aggravated mucosal damage. COX-1 appears to be the predominant source of prostaglandins in the human stomach albeit an upregulation of COX-2 in the presence of *H. pylori* infection [14, 15]. This may partly explain why *H. pylori* did not increase the risk of developing gastric ulcers among patients receiving rofecoxib [24]. However, the same study also indicated that rofecoxib did not reduce the risk of complicated duodenal ulcers in the presence of *H. pylori* infection. In addition, there was no advantage of rofecoxib over a nonselective NSAID for those with prior events and *H. pylori* infection in terms of the risk of clinical upper gastrointestinal events. Whether eradication of *H. pylori* will reduce the ulcer risk in these subgroups has not been investigated. In contrast, pooled analysis of data from randomized trials of celecoxib showed that *H. pylori* was a risk for ulcer disease in patients receiving nonselective NSAIDs but not in patients receiving celecoxib [23]. It is uncertain whether these contradictory

findings reflect differences in pharmacological properties, variations in study design or heterogeneity of *H. pylori*-infected patients. In animal models of gastric ulcer, COX-2 was upregulated in the granulation tissue and ulcer margin. Inhibition of COX-2 delayed healing of gastric ulcer in rodents. Limited data showed that COX-2 expression was increased in human gastric ulcer regardless of the *H. pylori* status. Whether inhibition of COX-2 will impair ulcer healing in the human stomach remains unknown. Future studies with pre-specified endpoints are needed to define the gastrointestinal risk of COX-2 inhibitors in different subgroups of *H. pylori*-infected patients.

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COX-2 Inhibition, *H. pylori* Infection and the Risk of Gastrointestinal Complications

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Abstract: Current data on the gastric safety of cyclooxygenase-2 (COX-2) inhibitors in the presence of *H. pylori* infection are largely derived from animal experiments and indirect clinical evidence. In animal models of *H. pylori* gastritis, COX-2 inhibitors suppressed prostaglandin synthesis and aggravated mucosal damage. In the human stomach, COX-1 appears to be the predominant source of prostaglandins despite the fact that COX-2 is upregulated in *H. pylori* gastritis. There are conflicting data on whether *H. pylori* alters the risk of ulcer in patients receiving COX-2 inhibitors. Among patients with *H. pylori* infection, rofecoxib reduced the risk of complicated gastric but not duodenal ulcers as compared to naproxen. The advantage of rofecoxib over naproxen also disappeared in patients with *H. pylori* infection and prior upper gastrointestinal events. In contrast, pooled data suggested that *H. pylori* increases the risk of ulcer in patients receiving nonselective nonsteroidal anti-inflammatory drugs but not in patients receiving celecoxib. In rodent gastric ulcers, COX-2 was upregulated in the granulation tissue and ulcer margin. Inhibition of COX-2 delayed healing of experimental gastric ulcer. Limited data showed that COX-2 expression was also increased in human gastric ulcer regardless of the *H. pylori* status. The functional significance of COX-2 in human gastric ulcer is unknown.

Key Words: *H. pylori*, cyclooxygenase-2, COX-2 inhibitors, prostaglandins, ulcer.

INTRODUCTION

Helicobacter pylori and nonsteroidal anti-inflammatory drugs (NSAIDs) are the two most important causes of gastroduodenal ulcer disease worldwide. Since many NSAID users are infected with *H. pylori*, it is important to determine whether *H. pylori* would influence the risk of developing ulcers in these patients. It is generally thought that *H. pylori* and NSAIDs are independent risk factors for ulcer disease because they damage the gastric mucosa via different mechanisms. *H. pylori* induces proinflammatory cytokines, leading to mucosal inflammation and epithelial injury. In contrast, NSAIDs damage the gastric mucosa by inhibiting gastric prostaglandin synthesis. However, this view may be simplistic because *H. pylori* and NSAIDs share certain pathways in the pathogenesis of mucosal injury [1, 2]. The controversy about the role of *H. pylori* in NSAID-associated gastroduodenal damage hinges on whether the effects of *H. pylori* and NSAIDs on gastric mucosal damage is synergistic, additive, or antagonistic, and whether there is sufficient clinical evidence to draw any conclusion. Current data suggest that *H. pylori* infection probably has a diverse effect on the gastric mucosa in different subgroups of NSAID users, which partly accounts for the conflicting results on the interaction between *H. pylori* and NSAIDs in mucosal damage [1, 2].

Development of NSAIDs that selectively inhibit cyclooxygenase-2 (COX-2) offers the prospect of relieving pain and inflammation without inflicting gastric injury. In healthy volunteers, selective inhibition of COX-2 does not suppress gastric prostaglandins [3]. There is good clinical evidence that COX-2 specific inhibitors cause fewer clinical upper gastrointestinal events compared with nonselective NSAIDs [4, 5]. However, the gastrointestinal safety of COX-2 specific inhibitors in the presence of mucosal inflammation remains unclear. COX-2 is induced in gastrointestinal inflammatory conditions, such as inflammatory bowel disease and *H. pylori* gastritis. Inhibition of COX-2 has been shown to suppress colonic prostaglandin synthesis in ulcerative colitis and Crohn's disease [6, 7]. In the rat colitis model, COX-2 specific inhibitor exacerbates colonic inflammation [8]. In the stomach, *H. pylori* induces mucosal inflammation and has been shown to upregulate the expression of COX-2 [1, 6, 7, 9, 10]. This raises the possibility that COX-2 may be the predominant source of prostaglandins in *H. pylori* gastritis, leading to an increased susceptibility to mucosal injury by COX-2 specific inhibitors. To date there are conflicting data showing that COX-2 specific inhibitors increase or have no effect on the risk of mucosal injury in the presence of *H. pylori* gastritis. How COX-2 specific inhibitors differ from nonselective NSAIDs in terms of their effects on *H. pylori*-infected gastric mucosa will be an interesting area of research.

Expression and Cellular Localization of COX-2 in *H. pylori* Infection

Many studies have reported an increased expression of COX-2 in the presence of *H. pylori* infection. *H. pylori* has been shown to upregulate the expression of COX-2 messenger RNA (mRNA) and stimulates prostaglandin synthesis in gastric cancer cell lines [11]. However, there are conflicting data on the cellular localization of COX-2 expression in *H. pylori* gastritis. Fu *et al.* reported that *H. pylori* induces COX-2 expression in the mononuclear

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inflammatory cells and myofibroblasts in the lamina propria [10]. However, other studies found that COX-2 was expressed mainly in the gastric epithelium [1, 6, 7]. Sawaoka *et al.* reported that COX-2 was expressed both in the gastric epithelium and subepithelial inflammatory cells in *H. pylori* gastritis [9]. These inconsistent immunohistochemical findings probably are related to different laboratory conditions and cross-reactivity of COX-2 antibodies with other mucosal antigens. Using in situ hybridization, it has been shown that *H. pylori* up-regulates the expression of COX-2 mRNA mainly in the gastric epithelial cells [1].

Role of COX-1 and COX-2 in *H. pylori*-Induced Prostaglandin Synthesis

In the normal human stomach, COX-2 is absent or minimally expressed whereas COX-1 is the source of prostaglandins that maintains the integrity of the mucosal barrier. This notion is consistent with the observation that in the absence of *H. pylori* infection, inhibition of COX-2 did not suppress gastric prostaglandin synthesis and inflicted minimal mucosal injury [3]. However, in cultured human gastric fibroblasts [12, 13], *H. pylori* induced the expression of COX-2 mRNA and increased prostaglandin synthesis. Indomethacin and a COX-2 inhibitor (NS-398) suppressed *H. pylori*-induced prostaglandin synthesis to the same extent. These findings suggested that COX-2 may substantially contribute to prostaglandin synthesis in *H. pylori* gastritis; and that selective inhibition of COX-2 may lose its gastric sparing effect in the presence of *H. pylori* infection.

However, there were conflicting data on the relative contributions of COX-1 and COX-2 in prostaglandin synthesis associated with *H. pylori* gastritis. Jackson *et al.* [14] reported that COX-1 and COX-2 were constitutively expressed in parietal cells of uninfected human stomach. Immunostaining for both COX-1 and COX-2 was increased in *H. pylori* gastritis. Interestingly, the increased *ex vivo* prostaglandin synthesis was significantly suppressed by a COX-1 inhibitor rather than a COX-2 inhibitor. Scheiman *et al.* studied the effect of rofecoxib on gastric prostaglandin synthesis in subjects with or without *H. pylori* infection [15]. Twenty *H. pylori*-infected and 6 uninfected healthy volunteers were treated with rofecoxib for 2 weeks. Although prostaglandin levels were increased in *H. pylori* gastritis, rofecoxib did not suppress prostaglandin synthesis in infected subjects. These results suggested that despite an upregulation of COX-2, *H. pylori* gastritis, COX-1 remains the predominant source of prostaglandins.

EFFECTS OF NSAIDS AND COX-2 SPECIFIC INHIBITORS ON *H. pylori*-INFECTED GASTRIC MUCOSA

Gastric prostaglandins play a crucial role in mucosal defense by regulating mucosal blood flow, mucus and bicarbonate secretion, epithelial proliferation, epithelial restitution, and mucosal immunocyte function [16]. The fact that *H. pylori* infection stimulates gastric prostaglandin production has led to the speculation that *H. pylori* may alleviate mucosal injury induced by NSAIDs. However, administration of NSAIDs to *H. pylori*-infected subjects has been shown to profoundly suppress prostaglandin production to levels that were similar to those of uninfected subjects [17, 18]. These findings indicate that the modest increase in prostaglandin levels induced by *H. pylori* is unlikely to have any important protective effect against NSAID injury. It has been postulated that the mucosal toxicity of *H. pylori*, which is largely mediated by inflammatory cytokines including interleukin (IL)-1, IL-6, IL-8 and tumor necrosis factor, is counterbalanced by protective responses, such as increased release of mucosal prostaglandins and hepatocyte growth factor [12]. Factors disturbing this balance may enhance the gastric damaging effects of NSAIDs and mucosal toxicity of *H. pylori* [12]. To date there are only a few experimental and human studies investigating the effects of selective COX-2 inhibition on *H. pylori*-infected gastric mucosa.

Animal Studies (Table 1)

Several studies have investigated the effect of nonselective NSAIDs and a COX-2 specific inhibitor on *H. pylori* gastritis using the Mongolian gerbil model [13, 19, 20]. In one study [13], COX-1 was detected in both normal and *H. pylori*-infected mucosa whereas COX-2 was expressed only in the infected mucosa. *H. pylori* infection increased prostaglandin synthesis. Indomethacin markedly inhibited prostaglandin synthesis in both normal and infected mucosa. NS-398 also suppressed prostaglandin synthesis in infected mucosa but did not have any effect on uninfected mucosa. Hemorrhagic erosions and neutrophil infiltration were found in *H. pylori* gastritis. These mucosal lesions were aggravated by indomethacin and NS-398. Both drugs potentiated the release of neutrophil chemokine and interferon-γ induced by *H. pylori*. In another study [19], indomethacin and NS-398 significantly suppressed gastric prostaglandin synthesis and there was a non-significant trend toward less severe suppression with NS-398 in *H. pylori*-infected gerbils. Indomethacin and NS-398 caused similar degree of gastric mucosal damage in infected animals despite

Table 1. Effects of NSAIDs and COX-2 Inhibitor on Animal Models of *H. pylori* Gastritis

Animal model	COX-1 & -2 expression	Baseline PGE2	PGE2 after NSAIDs	PGE2 after COX-2 inhibitor
Mongolian Gerbil [13]	COX-2 upregulated	Increased	Suppressed	Moderately suppressed*
Mongolian Gerbil [19]	---	Increased	Suppressed	Moderately suppressed†
Mouse [21]	COX-1 & -2 upregulated	Non-significant increase	Suppressed	Non-significant decrease

*Mucosal damage was aggravated by both NSAIDs and NS-398 in *H. pylori*-infected mucosa.
†NSAIDs and NS-398 induced similar degree of mucosal damage in *H. pylori*-infected animals.

different degrees of prostaglandin suppression. In contrast, there was an inverse relationship between gastric prostaglandin level and mucosal damage in uninfected animals. These findings suggested that while COX-2 specific inhibitors caused minimal injury to uninfected gastric mucosa, these drugs did not reduce mucosal damage in *H. pylori* gastritis.

Unlike the previous two studies, Kim *et al.* [21] found that both COX-1 and COX-2 were upregulated in mouse stomachs infected with *H. pylori*. *H. pylori* infection increased apoptotic index, cell proliferation index, neutrophil activity and the degree of chronic inflammation. There was a non-significant increase in gastric prostaglandin levels. All these changes were reversed after the administration of indomethacin whereas NS-398 did not induce a significant reduction. The result suggested that both COX-1 and COX-2 are induced by *H. pylori* infection. Induction of COX-1 also contributes to the increase in prostaglandin synthesis, mucosal cell turnover and inflammatory activity in *H. pylori* gastritis.

Recently, Futagami *et al.* [20] investigated how inhibition of COX-2 would influence the severity of NSAID-induced gastric damage in *H. pylori*-infected Mongolian gerbils. *H. pylori* infection induced COX-2 expression. Prolonged treatment with indomethacin caused more severe gastric damage in *H. pylori*-infected animals than in uninfected animals. Interestingly, pretreatment with NS-398 aggravated the mucosal damage induced by short-term treatment with indomethacin in the presence of *H. pylori*. The authors postulated that induction of COX-2 by *H. pylori* might protect the gastric mucosa against NSAID injury. Disturbance of this equilibrium state by inhibiting COX-2 may enhance the gastric toxicity of NSAIDs in *H. pylori*-infected animals (Fig. **1**).

Human Studies (Table 2)

Current evidence on the gastric safety of COX-2 inhibitors in *H. pylori*-infected patients is mostly derived from *post hoc* analysis. Whether *H. pylori* infection increases the risk of ulcer disease in patients receiving COX-2 specific inhibitors has generated conflicting results in the literature.

The influence of *H. pylori* infection on the risk of gastroduodenal ulceration was first reported in a subgroup analysis of a double-blind, 12-week endoscopic study of celecoxib versus naproxen [22]. Among patients who received celecoxib, the incidence of ulcer was 12.9% in patients with *H. pylori* infection compared with 2.9% in uninfected patients (P=0.023). Other risk factors included concurrent use of low-dose aspirin (P=0.001) and a history of ulcer (P=0.010). In contrast, *H. pylori* did not influence the risk of ulcer among patients who received naproxen. However, the same group of investigators reported contradictory results in a pooled analysis of four double-blind 12-week endoscopic studies of celecoxib that collectively enrolled 4000 arthritis patients [23]. Among patients who used nonselective NSAIDs, the incidence of ulcer was 28.4% in patients with *H. pylori* infection compared with 20% in uninfected patients (odds ratio 1.6 [1.1, 2.3]). Among patients who used celecoxib, the incidence of ulcer was 8.0% in patients with *H. pylori* infection compared with 5.1% in uninfected patients (odds ratio 1.6 [0.9, 2.8]). These results suggested that *H. pylori* is a risk factor for gastroduodenal ulceration in patients taking nonselective NSAIDs but not celecoxib.

In a multivariate analysis of risk factors for upper gastrointestinal clinical events [24] based on the data collected in the Vioxx Gastrointestinal Outcomes Research Study [5], major risk factors for the development of upper gastrointestinal clinical events included old age (≥75) and prior complicated or uncomplicated gastrointestinal events. Patients with prior gastrointestinal events who received naproxen had a high rate of clinical events regardless of *H. pylori* status. Although *H. pylori* was not considered as a risk factor in this multivariate analysis, two interesting findings were reported. First, patients in the rofecoxib group had

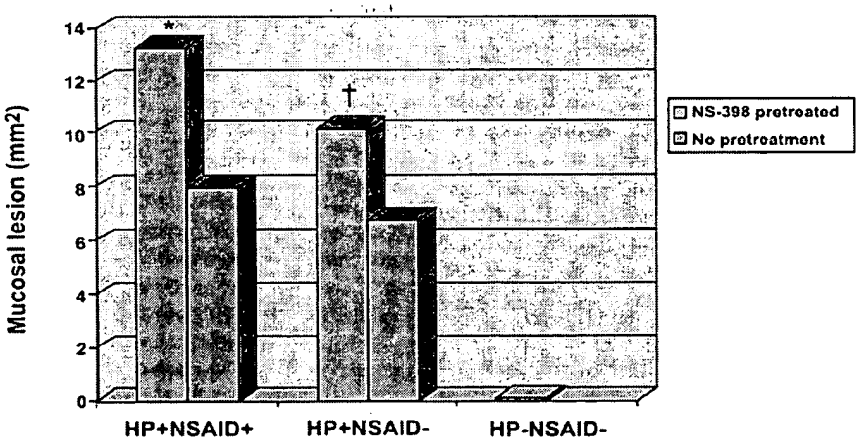

Fig. (1). Effects of Indomethacin on gastric damage in *H. pylori*-infected Mongolian gerbils with or without pretreatment with NS-398. HP and NSAID denote *H. pylori* and indomethacin, respectively. *P<0.05 versus HP+NSAID+ group without pretreatment with NS-398. †P<0.05 versus HP+NSAID- group without pretreatment with NS-398. Data derived from [20].

Table 2. Clinical Effects of *H. pylori* Infection on Gastroduodenal Damage of COX-2 Specific Inhibitors

Design	Number of patients	Outcomes			
Subgroup analysis of a 12-week RCT of celecoxib 400 mg versus naproxen 1 g [22]	536	Endoscopic ulcer:			
			Celecoxib	Naproxen	
		HP positive	12.9%*	29%	
		HP negative	2.9% (P=0.023)*	30%	
Pooled analysis of four 12-week RCTs of celecoxib 100-800 mg versus nonselective NSAIDs [23]	4000	Endoscopic ulcer (non-aspirin users):			
			Celecoxib	Nonselective NSAIDs	
		HP positive	8.0%	28.4%	
		HP negative	5.1%	20.0%	
		OR	1.6 (0.9 - 2.8)	1.6 (1.1 – 2.3)*	
Multivariate analysis of a RCT of rofecoxib 50 mg versus naproxen 1 g [24]	8076	Clinical upper GI events (per 100 patient-years):			
			Rofecoxib	Naproxen	
		Prior event, HP positive	12.18	14.00	RR 0.89 (0.38-2.07)†
		Prior event, HP negative	3.35	17.14	RR 0.20 (0.07-0.61)
		Complicated DU (per 100 patient-years):			
			Rofecoxib	*Naproxen*	
		HP positive	1.85	1.54	RR 1.20 (0.64-2.24)‡
		HP negative	0.34	1.41	RR 0.24 (0.09-0.64)

**H. pylori* was a risk factor in patients taking nonselective NSAIDs but not in patients taking celecoxib

†The upper GI sparing effect of rofecoxib was offset by the presence of *H. pylori* infection in patients with prior upper GI events.

‡The superiority of rofecoxib over naproxen in reducing the risk of complicated duodenal ulcers disappeared in the presence of *H. pylori* infection.

fewer gastric ulcers than patients in the naproxen group regardless of the *H. pylori* status. In contrast, rofecoxib did not reduce the risk of duodenal ulcers compared with naproxen among patients found positive for *H. pylori*. Second, among those with prior gastrointestinal events, the rate of events in the rofecoxib group was 3.5-fold higher in *H. pylori*-positive patients than in *H. pylori*-negative patients. The results suggested that the upper GI sparing effect of rofecoxib was the offset by the presence of *H. pylori* infection in patients with prior upper GI events, and the superiority of rofecoxib over naproxen in reducing the risk of complicated duodenal ulcers disappeared in the presence of *H. pylori* infection.

EFFECTS OF *H. pylori* ON ULCER HEALING ASSOCIATED WITH NSAIDS AND COX-2 SPECIFIC INHIBITORS

Whether *H. pylori* infection affects ulcer healing in patients receiving nonselective NSAIDs has yielded conflicting data. In the rat model, one study found that *H. pylori* attenuated the delay in ulcer healing induced by aspirin. This observation was attributed to suppression of acid secretion and stimulation of prostaglandin production by *H. pylori* [25]. However, there are conflicting findings about the effects of *H. pylori* on aspirin-induced gastric injury. The same group of investigators showed that *H. pylori* induced persistent mucosal bleeding in the rat stomach by impairing gastric adaptation to aspirin [18]. Eradication of *H. pylori* restores gastric adaptation to resist aspirin-induced injury. Hawkey *et al.* studied the effect of *H. pylori* eradication on gastroduodenal damage in chronic NSAID users with dyspepsia or ulcer [26]. In a subgroup of 41 patients with gastric ulcers, they found that eradication of *H. pylori* delayed ulcer healing (ulcer healing at 8 weeks: 72% in the eradicated group compared with 100% in the control group). In another randomized trial of *H. pylori*-positive patients with NSAID-associated ulcer bleeding, 195 patients (112 gastric ulcers and 83 duodenal ulcers) were randomly assigned to receive omeprazole or omeprazole plus eradication therapy for ulcer healing. Eradication of *H. pylori* did not have any significant adverse effect on the healing of gastric (*H. pylori*-positive versus *H. pylori*-eradicated: 94% versus 88%; p=0.29) or duodenal (*H. pylori*-positive versus *H. pylori*-eradicated: 100% versus 98%; p=1.0) ulcers [27] (Fig. 2). To date there is no definite evidence to show that eradication of *H. pylori* has any clinically important adverse effect on healing of NSAID-associated ulcers.

On the other hand, there are data suggesting that among patients receiving NSAIDs, gastric ulcers heal faster with *H. pylori* infection by acid suppression [28, 29]. *H. pylori* infection has been shown to augment the acid-suppressing effect of omeprazole [30, 31]. In a pooled analysis of three randomized trials of omeprazole for the prevention of mucosal injury in NSAID users [28], *H. pylori* appeared to enhance gastric ulcer healing by acid suppression but retard

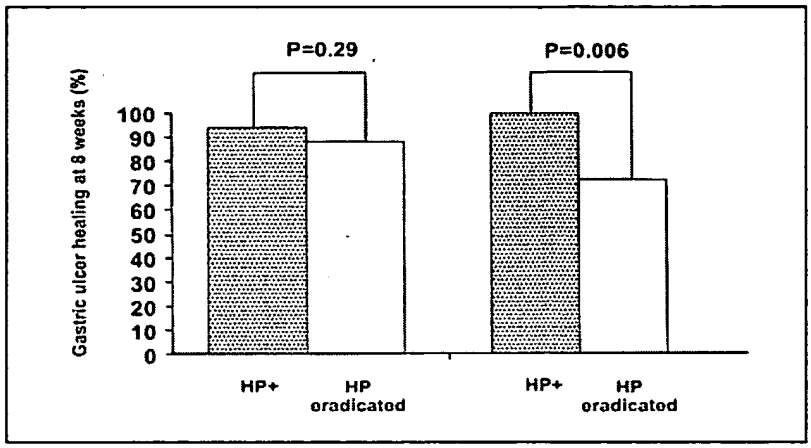

Fig. (2). Effects of *H. pylori* eradication on healing of gastric ulcers in patients receiving nonselective NSAIDs.

healing by misoprostol. However, the difference only reached statistical significance in patients receiving ranitidine (84% vs 51% at eight weeks) but not in patients receiving omeprazole. In another pooled analysis of two randomized trials of lansoprazole versus ranitidine in preventing NSAID-induced mucosal injury [29], gastric ulcer healing rates were significantly faster in *H. pylori*-positive patients than in uninfected patients though the difference was of doubtful clinical relevance (70% vs 61% at 8 weeks; $P < 0.05$).

Although COX-2 specific inhibitors inflict minimal gastric injury to the normal stomach, there is evidence from animal experiments that COX-2 may play a physiological role in restoring mucosal integrity. In the rat stomach, COX-2 was upregulated in acetic acid-induced gastric ulcers [32, 33]. COX-2 activity was detected in endothelial cells, macrophages and fibroblasts at the ulcer base [32, 33]. Selective inhibition of COX-2 has been shown to retard gastric ulcer healing [33-36]. Administration of NS-398 significantly retarded healing of acetic acid-induced ulcers in rats and thermal-cauterized ulcers in mice [33-35]. One study showed that inhibition of COX-2-derived prostaglandins in ulcerated mucosa delayed ulcer healing [33]. Other investigators found that angiogenesis and maturation of granulation tissue in gastric ulcer was impaired by inhibition of COX-2 [36]. Jones *et al.* [37] demonstrated that both nonselective NSAIDs and COX-2 inhibitors acted on endothelial cells to inhibit angiogenesis. In contrast, COX-1 was absent [36] or not induced in ulcerated mucosa [33, 34].

Unlike rodent ulcers, To *et al.* [38] found that both COX-1 and COX-2 were upregulated in human gastric ulcers. At the ulcer margin, increased COX-1 expression was detected in lamina propria cells whereas COX-2 was strongly expressed in the hyperplastic foveolar epithelium. At the ulcer base, COX-1 and COX-2 were strongly expressed in myofibroblasts, macrophages and endothelial cells in the granulation tissue. The findings were similar between *H. pylori* ulcers or NSAIDs ulcers. This raises the possibility that both isoforms of COX may contribute to ulcer healing in the human stomach regardless of the *H. pylori* status. However, other investigators found that although intense COX-2 immunoreactivity was detected in human gastric ulcers, there was no significant change in COX-1 expression in ulcerated mucosa [14, 39]. To date there is no clinical data as to whether COX-2 inhibitors would retard gastric ulcer healing.

CONCLUSION

Current data on the interaction between *H. pylori* infection and selective COX-2 inhibition with respect to gastric damage are mostly derived from animal experiments or indirect clinical evidence based on *post hoc* analysis. Several interesting findings deserve further studying. In animal models of *H. pylori* gastritis, COX-2 inhibitors suppressed prostaglandin synthesis and aggravated mucosal damage. COX-1 appears to be the predominant source of prostaglandins in the human stomach albeit an upregulation of COX-2 in the presence of *H. pylori* infection [14, 15]. This may partly explain why *H. pylori* did not increase the risk of developing gastric ulcers among patients receiving rofecoxib [24]. However, the same study also indicated that rofecoxib did not reduce the risk of complicated duodenal ulcers in the presence of *H. pylori* infection. In addition, there was no advantage of rofecoxib over a nonselective NSAID for those with prior events and *H. pylori* infection in terms of the risk of clinical upper gastrointestinal events. Whether eradication of *H. pylori* will reduce the ulcer risk in these subgroups has not been investigated. In contrast, pooled analysis of data from randomized trials of celecoxib showed that *H. pylori* was a risk for ulcer disease in patients receiving nonselective NSAIDs but not in patients receiving celecoxib [23]. It is uncertain whether these contradictory

findings reflect differences in pharmacological properties, variations in study design or heterogeneity of *H. pylori*-infected patients. In animal models of gastric ulcer, COX-2 was upregulated in the granulation tissue and ulcer margin. Inhibition of COX-2 delayed healing of gastric ulcer in rodents. Limited data showed that COX-2 expression was increased in human gastric ulcer regardless of the *H. pylori* status. Whether inhibition of COX-2 will impair ulcer healing in the human stomach remains unknown. Future studies with pre-specified endpoints are needed to define the gastrointestinal risk of COX-2 inhibitors in different subgroups of *H. pylori*-infected patients.

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